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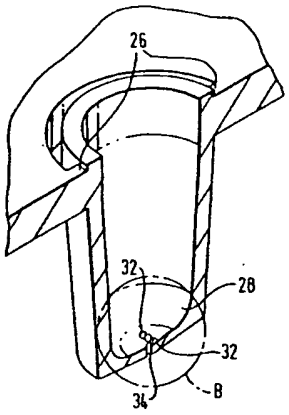
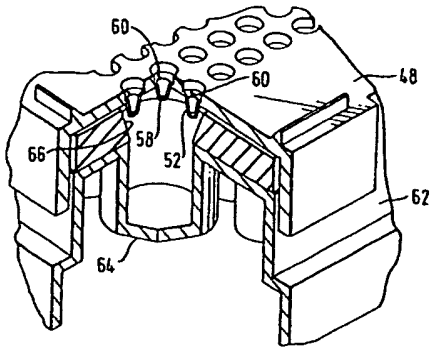
(54) Title: METHOD AND APPARATUS FOR TRANSFERRING AND COMBINING REAGENTS

(57) Abstract

The invention provides exemplary systems, methods, and apparatus for distinctly allocating liquids containing chemical compositions or compounds to known locations in an organized manner so that assays may be performed on the compositions, or so that the chemical compositions may be combined with other distinct chemical compositions or reagents prior to evaluation. In an exemplary embodiment, the invention includes a multiwell plate (12), for handling articles such as resins beads (32) suspended in a liquid. The plate (12) comprises a plurality of wells (16). The wells (16) in turn have a capillary hole (34) that is adapted to (i) retain articles in the well (16), and (ii) retain liquid in the well (16) while the liquid is not subjected to extrinsic forces, such as centrifugation or vacuum.





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METHOD AND APPARATUS FOR TRANSFERRING AND COMBINING REAGENTS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part application of U.S. Application Serial No. 08/887,141, filed July 2, 1997, which is a continuation-in-part application of U.S. Application Serial No. 08/753,808, filed December 2, 1996, both of which are herein incorporated by reference. This application is also a continuation-in-part application of U.S. Application Serial No. 08/868,689, filed December 2, 1996, herein incorporated by reference.

BACKGROUND OF THE INVENTION

This invention relates generally to the allocation of liquids containing various chemical compositions or compounds to locations where assays may be performed to evaluate the chemical compositions, or where the compositions may be combined with other substances, such as other chemical compositions or reagents, prior to evaluation. In one particular aspect, the invention is concerned with the analysis of chemical compositions which have been released from solid supports upon which the compositions were previously synthesized.

Processes for synthesizing various chemical compositions or compounds on solid supports, such as beads, are well known. For example, such processes are described in copending U.S. Application Serial No. 08/149,675, filed November 2, 1993 (Attorney Docket No. 16528J-004000) and 08/146,886, filed November 2, 1993 (Attorney Docket No. 16528J-000730), the disclosures of which are herein incorporated by reference. After synthesis, it is often desirable to analyze the compounds synthesized on the beads. One such process is by placing the beads into a plurality of wells containing a liquid. A portion of the compound on the beads is then released into the liquid.

Assays are then performed on the liquids containing the compounds to evaluate the compounds.

Before performing the assays, it is often desirable to separate the beads from the liquids containing the released compounds. One such method is by providing a plurality of wells having open bottom ends. A filter is placed near each open end, with the beads resting upon the filter. After the compounds have been released, the liquids are drained through the bottom ends, with the beads remaining on the filter.

Such a method for separating the liquids from the beads is undesirable for a variety of reasons. One particular drawback is that a significant amount of the liquid remains within the filter. This becomes particularly problematic as the volume of the wells becomes smaller, resulting in too little of the liquid being transferred from the wells. Another drawback is that such a method provides no convenient way for selectively removing only a portion of the liquid from the wells so that additional assays can be performed on the remaining liquids or so that the compounds can be combined with other compounds for further evaluation.

Hence, it would be desirable to provide systems and methods to efficiently remove all, or, in some cases, only a selected portion of the liquids from the wells so that assays may be performed on the liquids.

Another challenging aspect of evaluating compounds released from solid supports is the amount of time required to perform assays in order to evaluate a particular compound. For example, if each well contains only a single bead, separate assays must be performed on the liquid removed from each well. In some cases, throughput may be increased by placing a plurality of beads into a single well and releasing the compounds. Assays may then be performed on the liquids removed from the wells. For wells producing a positive result, each bead within the well must then again be tested to evaluate the compound. This usually employs synthesizing the same compounds on the beads, releasing the compounds, and again performing assays. Such a procedure is both burdensome and time consuming,

particularly if thousands of beads are involved in the process.

Hence, it would be further desirable to provide systems and methods for evaluating various compounds in a more efficient manner. It would be particularly desirable if such systems and methods effectively reduced the amount of time required to evaluate a particular compound. It would be further desirable if such systems and methods provided versatility so that various compounds may be combined with other substances prior to evaluation of the compounds.

SUMMARY OF THE INVENTION

The invention provides exemplary systems, methods, and apparatus for distinctly allocating liquids containing chemical compositions or compounds to known locations in an organized manner so that assays may be performed on the compositions, or so that the chemical compositions may be combined with other substances prior to evaluation. In some cases, the chemical compositions will be synthesized onto solid supports, such as beads. In such cases, the invention includes systems, methods and apparatus which facilitate both the handling of the solid supports and the release of the chemical compositions into the liquids prior to their allocation and subsequent evaluation.

In one exemplary embodiment, the invention provides a fluid transfer system which comprises a donor member having a plurality of separate regions. At least some of the regions contain at least one chemical composition, with each chemical composition being distinct or physically separated from any other chemical composition in the donor member. An acceptor member is also provided and includes a plurality of defined locations which are each adapted to receive a liquid medium. A transfer mechanism is provided to systematically transfer at least some of the chemical compositions from the donor member regions to at least some of the acceptor member locations such that the locale of each transferred chemical composition within the acceptor member is known. Further, each of the acceptor member locations has a volume that is less than about 500 µl. In this way, a large number of acceptor member locations may be

provided within a single system to efficiently transfer, in parallel fashion, large numbers of chemical compositions from the donor member to the acceptor member where evaluation or further processing of the chemical compositions may proceed.

The chemical compositions will preferably be included within a liquid medium when transferred. In one particular aspect, the chemical compositions will be transferred while the solid supports remain within the donor member regions. In another particular aspect, the transfer mechanism comprises a valve that is disposed within each region. The valve may be opened to allow the liquid medium to flow from the donor member to the acceptor member. In one embodiment, the regions comprise wells which each have holes in a bottom end. The holes are preferably sized to hold the chemical compositions within the wells by capillary forces. To transfer the liquid, the wells may be subjected to centrifugation or a differential pressure.

In another particular aspect, the chemical compositions are included on solid supports which are held within the donor member regions so that at least some of the chemical compositions may be released into the liquid medium prior to being transferred. Such solid supports may include, for example, beads having the chemical compositions synthesized thereon, the inner walls of wells to which photolithographic techniques have been applied to synthesize the chemicals thereon, the inner walls of wells into which a chemical has been placed to react with the walls of the wells (e.g., plastic walls), and the like. In still another aspect, the donor member, the transfer mechanism and the acceptor member are isolated from the outside environment. In this manner, evaporation of the chemical compositions from the system will be greatly reduced, thereby allowing smaller volumes of liquids to be employed.

In still a further aspect, the acceptor member locations comprise holding vessels into which a common reagent may be introduced and combined with the chemical compositions from the donor member regions. The common reagent in one aspect is directly introduced into each holding vessel by fluid delivery

lines. Alternatively, fluid delivery lines may be employed to interconnect various holding vessels so that several chemical compositions may be combined for analysis. In another alternative, the holding vessels may include a hole in a bottom end to facilitate the combination of several compositions from two or more holding vessels.

In yet another aspect, the acceptor member includes at least four locations per square centimeter. Preferably, the donor member regions each have a volume that is less than about 500 µl to correspond with the volume of the acceptor member locations. In one preferable aspect, each donor member region corresponds to each acceptor member region. Alternatively, more than one donor member region may correspond to a single acceptor member location.

In another embodiment, the invention provides a fluid transfer system which comprises a housing having at least one donor chamber which contains at least one chemical composition, that is held on a solid support. The housing further includes at least one acceptor chamber which is in fluid communication with the donor chamber. A transfer mechanism is employed to transfer at least some of the chemical composition from the donor chamber to the acceptor chamber. Further, the acceptor chamber has a volume that is less than about 500 µl.

In one particular aspect, the system includes a plurality of donor chambers and a plurality of acceptor chambers. Each acceptor chamber is in fluid communication with at least one of the donor chambers so that the chemical compositions, when held within a liquid medium, may be transferred between the chambers. In one exemplary aspect, the transfer mechanism comprises a centrifuge which spins the housing to transfer the chemical compositions from the donor chambers to the acceptor chambers. In another aspect, at least one of the donor chambers or the acceptor chambers includes a hole, and a pressure source is provided to transfer the chemical composition through the hole.

In another embodiment, the invention provides an exemplary method for combining distinct chemical compositions with

reagents. According to the method, the chemical compositions are organized into separate regions of a donor member so that each region includes a distinct chemical composition. At least some of the chemical compositions are systematically transferred to individual locations within an acceptor member such that the locale of each transferred chemical composition within the acceptor member is known. The individual locations are configured so that they define a volume that is less than about 500 µl. A reagent is introduced into each location having one of the chemical compositions for analysis of the compositions.

In one exemplary aspect, the same reagent is delivered to each location. In another aspect, the compositions are transferred by passing at least some of each of the chemical compositions through valves. Preferably, the valves comprise holes within the donor member regions to allow the chemical compositions to be passed through the holes by application of a differential pressure or centrifugation.

In another aspect, the chemical compositions are included on solid supports which are held within the donor member regions. With this arrangement, at least some of the chemical compositions are released into a liquid medium prior to transferring the chemical compositions to the acceptor member locations. Preferably, the acceptor member includes at least four locations per square centimeter to facilitate the transfer and evaluation of large numbers of distinct chemical compositions. Optionally, the donor member regions and the acceptor member regions may be organized into two dimensional arrays to further facilitate transfer and evaluation. In still another aspect, the donor member regions may be aligned with the acceptor member regions before transferring the chemical compositions. In some cases, more than one donor member region will be aligned with a single acceptor member location.

In another exemplary embodiment, the invention provides a method for combining distinct chemical compositions with reagents, where the chemical compositions are initially provided on a plurality of solid supports. The solid supports are organized into separate donor chambers so that each donor

chamber includes a distinct chemical composition. At least some of the chemical compositions are then systematically transferred to acceptor chambers which have a volume that is less than about 500 µl. The compositions are transferred in such a way that the locale of each transferred chemical composition within the acceptor member is known. A reagent is introduced to each acceptor chamber having one of the chemical compositions to evaluate the compositions.

In one exemplary aspect, the donor chambers and the acceptor chambers are included within a housing and are in fluid communication with each other. In this manner, the chemical compositions are transferred by spinning the housing. Preferably, at least some of the chemical compositions will be released into a liquid medium to facilitate the transfer of the chemical compositions to the acceptor chambers. In another aspect, at least some of either the donor chambers or the acceptor chambers include a hole, and a differential pressure is applied to the hole to transfer chemical compositions or reagents through the holes. In still another aspect, reagents are transferred from one acceptor chamber into another acceptor chamber or into one of the donor chambers.

Another exemplary device according to the invention comprises a multiwell plate for handling articles suspended in a liquid. The plate has a plurality of wells, with each well having a bottom end. A capillary hole is disposed in at least some of the wells. The capillary hole is sized to be both smaller than an individual article and to hold the liquid containing the released compound within the well. If the hole is static, or designed to always remain "open", the fluid may be retained in the well (i.e., prevented from exiting the hole) by capillary forces. Alternatively, if the hole is designed to open or increase the size of its opening (i.e., increase its limiting dimension) in response to an extrinsic force, the fluid may be retained in the well by virtue of the hole being closed or substantially closed. Either way, the liquid will be maintained within the well until an extrinsic force is applied to the liquid and/or well, causing at least some of the liquid

to exit the well. At the same time, the hole is designed or adapted to remain sufficiently small, even in an open configuration, so that the article will remain within the well after the liquid has been removed.

In one exemplary aspect, the capillary holes are disposed in bottom ends of the wells. Preferably, the bottom ends of the wells are tapered to an apex to facilitate easier handling of the articles. Preferably, the holes will be offset from the apex to help prevent an article from becoming lodged in the hole. By providing such a hole, substantially all the liquid may be transferred from the wells. Alternatively, the capillary holes may be disposed in sides of the wells. In this manner the device is configured so that a known portion of the liquid will be transferred from each well after the capillary forces are overcome. This is particularly advantageous in the event that additional assays need to be performed to evaluate a compound. By maintaining a portion of the liquid within the wells, the remaining liquid may be employed to perform any additional assays.

The hole may have a circular or non-circular profile. Holes having a non-circular profile are advantageous in that they are less-likely to become clogged with spherical articles, such as beads. Exemplary non-circular profiles include a triangular profile, a square profile, a slit, and a crack. Further, the holes are typically sized to exclude spheres larger than 500 μm, preferably 300 μm, more preferably 200 μm. The holes are also typically sized to allow the passage of spherical particles less than 5 μm, preferably less 10 μm. In a preferred embodiment, each well includes only a single hole. However, it will be appreciated that a small number of holes could be included in each well. The number of holes is typically less than 10, preferably less than 5.

The invention further provides an exemplary system for handling articles and comprises a top plate having a plurality of wells, with each well having a bottom end. A capillary hole is disposed in at least some of the wells. A bottom plate is further provided and includes a plurality of holding vessels.

The number of wells equals or exceeds the number of holding vessels such that when the top plate is positioned above the bottom plate, each well is aligned with at least one of the holding vessels. In this way, a fluid from each well may be transferred into a corresponding holding vessel.

In one preferable aspect, each well is aligned with a separate holding vessel. Alternatively, multiple wells may be aligned with a single holding vessel so that the liquid contained in multiple wells may be pooled into a single holding vessel.

The capillary hole will preferably have a size which is smaller than the articles and which will hold a liquid used to release the various compounds from the articles within the well by capillary forces. The capillary hole will preferably be disposed in the bottom ends of the wells, but may alternatively be disposed on sides of the wells so that only a portion of the liquid will be removed. In one alternative, the hole may be configured to be "transitory", meaning that the hole is normally biased closed until subjected to centrifugation or a vacuum which causes the hole to open.

The system may be provided with a centrifuge which spins the plates to overcome the capillary forces and transfer the fluids from the wells to the holding vessels. Alternatively, a vacuum source may be provided to draw the fluids through the capillary holes. In another alternative, fluids may be removed from the wells by placing an absorbent material against each of the well bottoms. The absorbent material will preferably be made of or be coated with a material which has a contact angle with water of less than 90°, so that the fluid in the well will be drawn through the holes and into the absorbent material. In this manner, fluids may be rapidly drained from the wells without the need for a centrifuge or vacuum manifold.

In an alternative aspect, the system further includes at least one reaction vessel, and a means is provided for transferring fluids from the holding vessels to the reaction vessel. One exemplary means for transferring comprises a plurality of pipettes. Preferably, each pipette will include a

capillary tube at its distal end so that a known quantity of fluid may be transferred from each holding vessel to the reaction vessel. In this manner, a portion of the fluids from the holding vessels may be transferred into the reaction vessel where assays may be performed.

The invention further provides an exemplary method for evaluating compounds which have been synthesized on solid supports. According to the method, a top plate is provided having a plurality of wells, each of which includes a capillary hole. A bottom plate is also provided having a plurality of holding vessels. At least one article is introduced into some of the wells, with the article having a compound included thereon. The compound is then released from each article, and at least a portion of the released compounds are transferred through the capillary holes and into at least one of the holding vessels of the bottom plate. Assays are then performed on the compounds transferred from the wells to evaluate the compounds.

In one aspect of the method, only a single article is introduced into each well. With this arrangement, the released compound in each well may be transferred into a separate and corresponding holding vessel (i.e. a holding vessel which is aligned with only one well). Alternatively, the compounds in a plurality of wells may be pooled and transferred to a single holding vessel to form a combined compound within the holding vessel.

If the released compound in each well is transferred into a separate and corresponding holding vessel, substantially all of the released compound will preferably be transferred from each well. A portion of the compounds in each of the holding vessels may then be transferred into reaction vessels to form combined compounds within the reaction vessels. The assays are then performed on the combined compounds within the reaction vessels. If a positive result is produced with the assay on the combined compound, additional assays may then be performed on the compounds remaining in the corresponding holding vessels. In this way, the time required to evaluate the compounds may be greatly reduced since, if a positive result is not produced with

the assay on the combined compound in the reaction vessel, it will not be necessary to perform individual assays on the compounds within each holding vessel. Further, if a positive result is produced in a reaction vessel, additional compounds do not need to be released from the articles since a portion of the removed compound will remain in each holding vessel and will be available for analysis.

If the released compound within some of the wells is transferred into a single holding vessel to form a combined compound, it is preferable to transfer only a portion of the released compound to the holding vessel. Assays may then be performed on the combined compound in the holding vessel. If a positive result is produced with the assay on the combined compound, additional assays may then be performed on the compounds remaining in each well. Alternatively, the released compounds within multiple wells may by pooled into two or more holding vessels to form a variety of combined compounds.

In an alternative aspect of the method, multiple articles are introduced into each of the wells. With this arrangement, the released compound in each well may be transferred into a separate and corresponding holding vessel, or the compounds from a plurality of wells may alternatively be pooled and transferred into a single holding vessel to form a combined compound. If the released compound in each well is transferred into a separate and corresponding holding vessel, assays will then preferably be performed within the holding vessels. Alternatively, the compounds within a plurality of holding vessels may be transferred into a reaction vessel to form a combined compound within the reaction vessel. Assays may then be performed on the combined compound within the reaction vessel. If a positive result is produced with the assay on the combined compound, additional assays may then be performed on remaining compounds within the holding vessels. This procedure increases throughput since only one assay may need to be performed on the combined compound within the reaction vessel if a positive result is not produced.

If the compounds within the wells are pooled into a single

holding vessel to form a combined compound, only a portion of each compound will preferably be transferred from the wells. Assays may then be performed on the combined compound in the holding vessel. If a positive result is produced with the assay on the combined compound, additional assays may be performed on the compounds remaining in each well.

To remove only a portion of the released compounds from the wells, the capillary holes will preferably be provided on sides of the wells. The top plate may then be spun to transfer the portion of the released compounds from the wells. In an alternative aspect, the capillary holes may be placed at the bottom end of the wells and the wells may then be spun to centrifuge the released compounds through the capillary holes. By providing the holes at the bottom end of the wells, preferably substantially all of the liquid will be transferred from the wells by the centrifuge process.

When transferring the compounds from the holding vessel to the reaction vessel, a pipetting system will preferably be employed. In this manner, a known volume of the compounds may be transferred from each holding vessel into the reaction vessel.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic view of an exemplary system for allocating chemical compositions from a donor member to one or more acceptor members in order to facilitate evaluation of the compositions according to the invention.

Fig. 2 is a flow chart illustrating one exemplary method for operating the system of Fig. 1 according to the invention.

Fig. 3 is a perspective view of an exemplary system for separating a liquid from a plurality of solid supports upon which various compounds have been released into the liquid according to the present invention.

Fig. 4 is a cross-sectional side view of a portion of the system of Fig. 3.

Fig. 5 is a perspective view of a plurality of wells containing solid supports from the system of Fig. 3.

Fig. 5A is a more detailed view of one of the wells of Fig. 5 taken along lines A-A.

Fig. 5B is a more detailed view of a bottom end of the well of Fig. 5A taken along lines B-B.

Fig. 5C is a more detailed view of the bottom end of the well of Fig. 5B showing a hole offset from the apex of the well bottom.

Fig. 5D is a cross sectional side view of an alternative well design having a transitory hole which remains closed until centrifuged.

Fig. 5E illustrates the well of Fig. 5D when centrifuged to open the hole.

Fig. 5F illustrates the wells of Fig. 5 having an absorbable material placed in contact with the bottom ends to remove liquids from the wells.

Fig. 6 illustrates a bottom plate of the system of Fig. 3 having a plurality of holding vessels and a pipetting system for transferring fluids from the holding vessels according to the present invention.

Fig. 7 is a perspective view of a plate having a reaction vessel for receiving liquids transported by the pipetting system of Fig. 6 according to the present invention.

Fig. 8 is a perspective view of an alternative system for separating fluids from solid supports according to the present invention.

Fig. 8A is a more detailed view of the system of Fig. 8 taken along lines A-A.

Fig. 8B is a cross-sectional side view of a well and a holding vessel of the system of Fig. 8A.

Fig. 9 is a perspective view of still another alternative system for separating fluids from solid supports according to the present invention.

Fig. 9A is a more detailed view of the system of Fig. 9 taken along lines A-A.

Fig. 10 is a cross-sectional side view of a portion of an alternative bottom plate which may be used with the system of Fig. 9.

Fig. 11 illustrates an exemplary process for constructing well plates having capillary holes therein according to the invention.

DETAILED DESCRIPTION OF THE SPECIFIC EMBODIMENTS

I. Definitions

The term "extrinsic forces", when used with respect to forces applied to the well of a microtiter plate and/or to fluid therein, is understood to mean forces which can be used to drain the fluid from a well having a capillary hole therein (a "pierced well"), where the capillary hole is sized to retain the fluid in the absence of such extrinsic forces. Examples of extrinsic forces include a vacuum applied to a sealed space underneath a microtiter plate containing such pierced wells. Upon application of the vacuum, the drop in pressure overcomes the forces (e.g., capillary forces) retaining the fluid inside the well, and draws the fluid through the capillary hole, typically into a second plate having a plurality of holding vessels aligned with the pierced wells. Extrinsic forces may also be provided by spinning the plates in a centrifuge, or by contacting a piece of absorbent material with the capillary hole. In the latter case, fibers from the material come into contact with the fluid at the outside edge of the capillary hole and "wick" it away, thus drawing the fluid from the well.

The term "capillary hole" as used herein refers to a discrete opening, typically in the well of a microtiter plate, that is small enough so that under conditions where the well contains fluid which covers the hole, the fluid is prevented from escaping through the hole. In cases where the hole is "static", i.e., is not designed to deform between "closed" and "open" positions upon application of an extrinsic force, the fluid is prevented from exiting the hole by capillary forces. However, if an extrinsic force tending to force or pull the fluid through the hole is applied to the fluid, and the force is greater than the capillary forces serving to keep the fluid in the well, the fluid will flow through the capillary hole.

A capillary hole can have a circular or non-circular

profile. A circular profile can be achieved using, for example, a round needle, such as a standard sewing needle. A non-circular profile can adopt any of a wide variety geometries, ranging from an oval to an irregular shape to a long, thin crack. Exemplary non-circular profiles include a triangular profile, which can be made using a needle that had been ground down to have a triangular cross-section. Similarly, a "slit" capillary hole can be made with a razor blade or scalpel.

The term "capillary hole" is understood *not* to apply to filters, frits, or similar devices which rely on a meshwork of non-discrete pores to separate solids from liquids. The size of a capillary hole may be defined in terms of its "limiting dimension". The limiting dimension refers to the shortest distance from one edge of the hole to the other measured through the center of the region where the hole has the largest cross-sectional area for passing a spherical particle. The limiting dimension is thus equal to the diameter of the largest sphere that can pass through the hole. The limiting dimension is thus adjusted to retain the smallest articles that the practitioner desires remain in the well. Exemplary limiting dimensions for capillary holes used with the present invention are typically less than about 500 μm, preferably less than about 300 μm, more preferably less than about 200 μm. The limiting dimensions are preferably greater than about 5 μm, more preferably greater than about 10 μm.

II Compound Processing Systems

The invention provides systems, methods and apparatus which are useful in helping to evaluate or identify various chemical compositions or compounds, particularly those which have previously been synthesized on solid supports, such as members of a combinatorial library of compounds. In particular, the invention provides for the distinct allocation of liquids which contain chemical compositions to known locations so that the chemical compositions may be assayed or combined with other substances or reagents, such as other chemicals, particles, microorganisms, cells, and the like, for further evaluation. In

cases where the compositions are included on solid supports, the invention also provides for the release of the compositions from the solid supports into a liquid. Following the release of the compositions, the liquids which now contain the compositions are separated from the solid supports so that the liquids may be allocated and evaluated. Such solid supports may include, for example, beads or membranes having the chemical compositions synthesized thereon, the inner walls of wells to which photolithographic techniques have been applied to synthesize the chemicals thereon, the inner walls of wells into which a chemical has been placed to react with the walls of the wells (e.g., plastic walls), and the like.

Beads to which the chemical compositions may be synthesized are usually constructed of a polymer such as polystyrene and polyethylene glycol, and are commercially available from, for example, Nova Bio-Chem. The beads typically have diameters on the order of about 5μm to about 300μm, more usually from about 80μm to about 200μm.

To release the various compounds from the beads, the beads are usually placed in wells in the presence of a liquid medium, such as water, ethanol, methanol, buffer, DMSO, trifluoroacetic acid (TFA), and the like. The various compounds may then be released from the beads using any of a variety of processes, such as by photolysis, where they will be contained within the liquid medium.

In addition to providing for the separation of the liquids from the solid supports, the invention also provides various ways of increasing throughput so that greater numbers of compounds can be analyzed in a shorter amount of time. In some cases, throughput may be increased by decreasing the size of wells or chambers which are employed to store the liquids. For example, the volume of such wells or chambers will preferably be 500 μl or less, and more preferably about 100 μl or less, so that large numbers of wells or chambers may be organized into a single device or plate. Such a plate typically contains about 100 or more wells. Preferably, the invention will include at

least four wells or chambers per square container. In this way, large numbers of evaluation processes may proceed in parallel to greatly reduce the time required for evaluating large numbers of distinct chemical compositions.

Throughput is also increased by providing efficient transport mechanisms to transfer the various fluids from location to location. For example, when wells or chambers are employed to hold the fluids, the wells may be interconnected with various valves (including micro-valves), tubing (or other fluid paths), by stacking the wells, and the like. In this way, the fluids may be systematically transferred from location to location using gravity, centrifugation, the application of positive or negative pressure, and the like.

Another advantage of the invention is that other fluids containing various substances may be introduced to any location within the system at any time to facilitate evaluation of the compounds. In this way, fluids containing other substances may be rapidly combined with the compounds in parallel fashion to facilitate evaluation.

In some cases, the wells will be open to facilitate easy introduction of various chemicals, substances, reagents, and the like into the wells. In other cases, the entire system will be closed, with the various fluids and substances being injected into the system without exposing the system to the outside environment. Closing of the system in this manner is particularly advantageous as volume sizes are decreased to help prevent evaporation of the fluids, and if an inert atmosphere (*e.g.*, argon or nitrogen) is desired to be maintained.

Referring now to Fig. 1, an exemplary system 1 for systematically transferring various distinct fluids to various known locations for evaluation will be described. System 1 comprises a donor member 2 and a plurality of acceptor members 3A and 3B, it being appreciated that additional acceptor members may also be included. Donor member 2 may be integrally formed with acceptor members 3A and 3B, or, alternatively, each of the various members may be removably attached to each other. Donor member 2 includes a plurality of regions R which are each

configured to receive a distinct chemical composition. By "distinct" it is intended to mean that chemical compositions, such as, for example, compositions originating from solid supports, a collection of solid supports, and the like, are physically separated from each other when within a given region. One exemplary way for handling the chemical compositions is to synthesize them onto solid supports and then to place the solid supports into regions R (or to synthesize the chemical compositions directly onto regions R). Optionally, the chemical compositions may be externally input into regions R as shown.

Each region R is in fluid communication with a location L of acceptor member 3A. In some cases, each region R will be in fluid communication with only a single location L. Alternatively, system 1 may be configured so that each region R is in fluid communication with any or all of the locations L of acceptor member 3A. In this way, distinct chemical compositions may be transferred from regions R to any one, or a combination, of locations L. It will be appreciated that the transfer of the fluids having the chemical compositions will be regulated so that the final resting place of each chemical composition with the locations L will be known. Preferably, the chemical compositions will be transferred from the donor member regions (after being released from their solid supports) while the solid supports remain within the donor member regions. In this manner, the evaluation process is facilitated by providing an efficient way to separate the chemical compositions from the solid supports and to place the chemical compositions in known locations where analysis may occur.

As shown, acceptor member 3B also includes a plurality of locations L which may be configured to be in fluid communication with any of locations L of acceptor member 3A or regions R of donor member 2. In this way, fluids may be transferred in any direction between regions R, locations L of acceptor member 3A, and locations L of acceptor member 3B. The number of possible combinations may be increased by simply increasing the number of regions R and locations L.

Each of locations L will preferably include a substance

that will be combined with the chemical compositions from the regions R in order to prepare the chemical compositions for evaluation or to begin the actual evaluation process. Such substances may be pre-stored within the locations L or may be input externally, as shown. Exemplary substances which may be stored and/or input include reagents, other chemical compositions, particles, microorganisms, cells, scintillant proximity assay (SPA) beads, and the like.

System 1 may be configured to be either an open system or a closed system. When open, the regions R and locations L will preferably comprise open wells into which substances may be directly introduced. When closed, each of the regions R and locations L will be interconnected by micro-channels, by stacking the regions R over locations L, or the like. Various valves, including micro-valves, capillary holes, and other valves as described hereinafter, may be employed to regulate the transfer of fluids between the regions R and locations L using gravity, centrifugation, the application of positive or negative pressure, and the like. Further, external input sources will be provided for introducing various reagents, chemical compositions, and the like into the system through fluid paths or micro-channels without exposing the system to the outside environment. In this way, the possibility of contamination and evaporation of the fluids will be greatly reduced. It will be appreciated that fluid introduction and transfer into and within the system may be controlled with a processor, e.g., to control application of pressure, the opening of valves, and the like.

Referring now to Fig. 2, an exemplary method for evaluating chemical compounds using the system of Fig. 1 will be described. Initially, chemical compounds are distinctly placed into the receptor locations or regions R of donor member 2. At least some of the compounds are transferred from the regions R to locations L in the acceptor member 3A such that it is known where each compound resides. Assays may then be performed on the compounds within the locations L by combining the compounds with a reagent. Optionally, additional assays may be performed by adding additional reagents. If desired, the compounds may be

transferred to other locations, such as in acceptor member 3B, for evaluation.

Sometimes, it will be desirable to combine the compounds with other substances, including other compounds, particles, microorganisms, cells, and the like. This may occur either before or after various reagents have been added. If so, the method provides for the addition of such substances. Additional assays may then be performed on the compounds. Optionally, the compounds may be transferred to other locations L or regions R within the system to facilitate the additional of various substances or for evaluation.

A. Systems Using Pierced Multi-Well Plates

Referring now to Fig. 3, one exemplary system 10 for evaluating various chemical compounds will be described. System 10 is particularly useful in cases where compounds have been released from beads into a liquid medium. System 10 includes a top plate 12 and a bottom plate 14 (which may also function as an intermediate plate as described hereinafter with reference to Figs. 4 and 5). Top plate 12 includes a plurality of wells 16 into which the beads and liquid medium are placed. As shown, top plate 12 includes 96 wells which are fashioned to be compatible with commercial processing equipment as is known in the art. However, it will be appreciated that any number of wells may be provided as required by a given procedure. Conveniently, clearance cuts 18 and 20 are provided to facilitate robotics employed to handle the plate.

Referring now to Fig. 4, construction of system 10 will be described in greater detail. Top plate 12 rests on bottom plate 14, with wells 16 of top plate being received into a plurality of holding vessels 22 in bottom plate 14. Each well 16 in top plate is received into a separate and corresponding vessel 22 in bottom plate 14. For example, if top plate 12 includes ninety-six or 864 wells, bottom plate 14 will include ninety-six or 864 holding vessels 22 so that each well 16 will be received into a separate holding vessel 22 when top plate 12 is placed on bottom plate 14. Top plate 12 may easily be separated from bottom

plate 14 by lifting top plate 12 from bottom plate 14. In this manner, after a liquid medium has been transferred from wells 16 to holding vessels 22, plates 12 and 14 may be separated from each other so that the liquid medium can be further analyzed.

Bottom plate 14 will preferably be sized so that it is compatible with commercially available handling and processing equipment. Preferably, wells 16 will be detachable from top plate 12 to further aid in the analysis of the articles retained therein. The volume between the bottom of wells 16 and a bottom end of holding vessels 22 will be sufficient so that it may receive the entire volume of liquid transported from wells 16.

Referring to Figs. 5 and 5A-5C, construction of wells 16 to facilitate the separation of liquids from the beads will be described in greater detail. As shown in Fig. 5, the wells may conveniently be provided in a strip 24, with eight wells being included in each strip. Wells 16 are preferably connected to strip 24 at tabs 26 so that wells 16 may be conveniently detached from strip 24 when needed. This construction also permits vapors from the fluid in each holding vessel 22 to escape without being trapped under a solid cover and diffusing over other holding vessels, which minimizes the potential for cross-vessel contamination when volatile reagents, such as TFA, are used.

As best shown in Figs. 5A-5C, each well 16 is tapered at a bottom end 28 to form an apex 30. In this manner, a plurality of beads 32 will tend to settle in bottom end 28 near apex 32. Laterally offset from apex 30 is a capillary hole 34 through which a liquid medium may be transferred into holding vessels 22 of bottom plate 14.

Capillary hole 34 will preferably be sized to be smaller than beads 32. The size of capillary hole 34 will also be configured such that it may hold a liquid medium within wells 16 by capillary forces when the liquid is not subjected to extrinsic forces. The size of capillary hole 34 may vary substantially depending upon the type of liquid medium and the size of beads 32. In general, the hole will have a limiting dimension (diameter in the case of round holes) that is between

about 25% and about 75% of the bead diameter, preferably between about 40% and 60% of the bead diameter. For example, for beads with a size range from about 150μm to about 250μm, a preferred limiting dimension is in the range from about 80μm to about 100μm.

Capillary hole 34 may adopt any selected geometry, so long the hole is sized smaller in at least one dimension (the limiting dimension) than the diameter of the smallest bead that is desired to be retained in the well. For example, the hole may adopt a rectangular cross-section as viewed from the top of the well, with a length that may be longer or shorter than the bead diameter, but with a width (here, the limiting dimension) that must be shorter than the bead diameter.

Non-circular hole cross-sections are particularly advantageous in that they are less likely than circular holes to become plugged or clogged with beads during use. As can be appreciated, a round hole having a diameter that is smaller than a bead diameter can be completely occluded by a spherical bead centered on top of the hole. In contrast, a hole having a non-circular cross-section is not easily occluded -- regardless of how the bead settles, there will be a part of the hole through which liquid can bypass the bead and escape. Exemplary non-circular cross-sections include triangular holes and slits.

As best shown in Fig. 5C, capillary holes having a circular cross-section, such as capillary hole 34, are preferably offset laterally from apex 30 so that beads 32 will not tend to settle over capillary hole 34, thereby preventing the liquid medium from being transferred through capillary hole 34. Although it is preferred to have only a single capillary hole 34, additional capillary holes may optionally be provided in bottom ends 28.

To draw the liquid medium through capillary hole 34, a centrifuge may be employed. In this manner, top plate 12 and bottom plate 14 may be spun at a rate which is sufficient to overcome the capillary forces and to draw the liquid medium from wells 16 into holding vessels 22. Alternatively, a vacuum may

be provided at bottom ends 28 of wells 16 to draw the liquid into holding vessels 22.

When employing a centrifuge or a vacuum, wells 16 may optionally be modified so that the capillary holes are configured to be transitory holes 34' as shown in Figs. 5D and 5E. As illustrated in Fig. 5D, transitory holes 34' are normally biased closed. This is best accomplished by constructing bottom ends 28 of a flexible material which is normally biased toward the interior of wells 16. In this manner, holes 34' are normally closed to prevent fluids from draining. Upon centrifugation or application of a vacuum, holes 34' flex open as shown in Fig. 5E to allow transfer of the liquids. After centrifugation, holes 34' will again close.

As illustrated in Fig. 5F, liquids may be drained from wells 16 without the need for a centrifuge, vacuum manifold or other complex or expensive accessory. Instead, drainage may be accomplished by placing a strip of an absorbent material 35 in contact with bottom ends 28. The absorbable material will preferably have a capillary force which is higher than the capillary force of holes 34 so that liquids within the wells will be drawn by a wicking action into the absorbable material 35. Exemplary materials for the absorbable material comprise paper, glass fiber mat, synthetic fiber mat, polymer fibers, a polymer acrylic acid gel, or the like.

Another advantage of employing absorbable material 35 to remove the liquids is that the liquids may rapidly and easily be drained from the wells. This allows reagents, washing fluids, waste fluids and the like to be removed quickly so that the solid supports may be rapidly subjected to various fluids during the process of synthesis or compound removal, thereby making the system more conducive to quick assay protocols. Further, useful compounds may be wicked into an organized array or onto a solid support such as a filter so that subsequent procedures may be performed using equipment compatible with samples in arrayed formats.

One particular advantage of providing capillary hole 34 in bottom end 28 is that unlike, e.g., filters, substantially all

of the liquid medium within wells 16 may be transferred into holding vessels 22. Since substantially all the liquid medium may be transferred without waste, the amount of liquid medium required to adequately perform the desired assays can be greatly reduced.

System 10 may be employed in a variety of ways to evaluate compounds synthesized on beads 32. For example, each well 16 may be provided with a single bead or with multiple beads. If a single bead is included in each well (and a portion of the compounds is released into a liquid medium), the liquid medium having the released compound may be transferred through capillary hole 34 into holding vessels 22. Assays may then be directly performed on the liquid medium within holding vessels 22. Since bottom plate 14 is configured to be compatible with commercial processing equipment, such assays may be rapidly and conveniently performed.

A similar process may also be employed if multiple beads are included in each well 16. If a positive result is identified in one of holding vessels 22, it may be concluded that one of beads 32 within the corresponding well 16 will have the bead containing the compound which produced the positive result. The beads may then be re-assayed individually if a portion of the compound remained with the beads, or they may be decoded (to determine what compounds they contained), after which the compounds can be synthesized and assayed individually. Separate assays may then be performed on those beads to evaluate the particular compound. In this way, throughput is increased since multiple beads may be analyzed at the same time.

To further increase the throughput of system 10, bottom plate 14 may be configured as an intermediate plate as illustrated in Fig. 6. In this manner, after the liquid medium is transferred into bottom plate 14 as previously described, top plate 12 is removed and the liquid medium from several holding vessels is pooled into a separate reaction vessel 36 in a plate 38 as illustrated in Fig. 7. Assays may then be performed on the mixture within reaction vessel 36 to see if a positive result is produced. A particular advantage of this method is

that if a positive result is identified in reaction vessel 38, additional assays may be performed on the liquid medium remaining within holding vessels 22 of bottom plate 14. This approach enables increased throughput without the need to prepare additional beads with synthesized compounds in order to evaluate a particular compound.

To remove only a portion of the liquid medium from holding vessels 22, a pipetting system 40 is provided as shown in Fig. 6. Pipetting system 40 includes a plurality of pipettes 42 which each include a capillary tube 44 at a distal end. As shown, system 40 includes nine pipettes 42 so that the liquid medium within nine holding vessels 22 may be pooled within reaction vessel 36. However, it will be appreciated that the number of pipettes 42 may vary depending on the particular application. Capillary tubes 44 are advantageous in that a known quantity of the liquid medium will be drawn into each capillary tube so that a known volume of liquid from each holding vessel 22 may be transferred into reaction vessel 36.

Reaction vessel 36 will be useful when either a single bead or multiple beads are placed within wells 16 and the compounds released. For example, if a single bead is provided in each well and a positive result is produced in reaction vessel 36, assays may then be performed on the liquid medium remaining within the nine holding vessels 22 from which the combined liquid was pooled. In this way, the compound may be identified by noting which holding vessel 22 produces a positive result.

If multiple beads 32 are included in each well and a positive result is identified in reaction vessel 36, assays may then be performed on the liquid medium held within the nine holding vessels 22 from which the combined liquid was pooled. If a positive result is produced in one of holding vessels 22, separate assays will need to be performed on the compounds included on each bead placed in the corresponding well 16.

Referring now to Fig. 8, an alternative system 46 for separating a liquid medium from beads will be described. System 46 includes a top plate 48 and a bottom plate 50. Similar to

system 10, plates 48 and 50 are configured to be compatible with commercially available process and handling equipment. Top plate 48 includes 864 wells 52 (only a portion of which are illustrated). Alternatively, other numbers of wells 52 may be included in top plate 48, such as by including 96 wells. Further, different shapes and sizes of plates may be possible.

As best shown in Figs. 8A and 8B, each well 52 in top plate 48 is aligned with and received into a corresponding holding vessel 54 in bottom plate 50. Top plate 48 rests on bottom plate 50 so that the plates may be separated to perform assays on a liquid medium transferred from wells 52 to holding vessels 54.

Each well 52 includes a curved bottom end 56 into which beads 58 may be placed. As described hereinafter, each well 52 may receive either a single bead or a plurality of beads. Included on the side of each well 52 is a capillary hole 60. Capillary hole 60 may be configured with the same dimensions as capillary hole 34 of system 10 as previously described. An advantage of placing capillary hole 60 on the side of well 52 is that only a portion of the liquid medium contained in each well may be transferred into holding vessels 54. In this manner, if a positive result is produced when performing assays on the liquid medium within holding vessels 54, a portion of the liquid medium having the released compound will remain within wells 52 so that additional assays may be performed to evaluate the specific compound. This procedure will be most useful when multiple beads 58 are included in each well 52. To transfer a liquid medium through capillary hole 60, plates 48 and 50 may be spun to centrifuge a portion of the liquid medium from wells 52 and into holding vessels 54.

Referring to Figs. 9 and 9A, system 46 may be modified so that top plate 48 rests upon a bottom plate 62 having ninety-six holding vessels 64. Conveniently, a spacer plate 66 is provided between top plate 48 and bottom plate 62 to appropriately space the distance between wells 52 and holding vessels 64. Spacer plate 66 also serves to channel fluids from wells 52 into holding vessels 64. As shown, each holding vessel 64 is aligned

with nine wells 52 so that the liquid medium contained within the nine wells may be pooled into a single holding vessel. Assays may then be performed upon the pooled liquid within the holding vessels 64. If a positive result is produced, the liquid remaining within wells 52 may be further analyzed to evaluate the compound as previously described. In this manner, a high throughput system is provided since the compound from multiple beads may be evaluated in a single step. Further, since a portion of the liquid medium is maintained within wells 52, additional assays may be performed without having to separately release additional compounds from the beads.

Top plate 48 may alternatively be employed with bottom plates having holding vessels with a variety of configurations. One such bottom plate 68 is illustrated in Fig. 10. Top plate 48 includes wells which may be removed from plate 48 to facilitate handling and testing. The V-shape in the bottom of holding vessel 70 is advantageous for retrieving all of the liquid.

B Construction of Pierced Multiwell Plates

Referring now to Fig. 11, an exemplary system 80 and process for rapidly and inexpensively constructing a multi-well plate having capillary holes therein (such as with wells 16 and holes 34) will be described. System 80 comprises a rack 82 which holds a plurality of test tubes 84. Rack 82 may be constructed from, for example, an insert from a box of microliter pipette tips. Tubes 84 may be any size of commercially available test tube, such as, for example, 0.5 ml polypropylene test tubes. Tubes 84 are placed into rack 82 as shown and a sheet of plastic 86 is placed on top of tubes 84. Sheet 86 is then softened with heat and a commercially available vacuum mold (not shown) is employed to draw sheet 86 into the mold.

Holes may be formed in each well by punching, such as with a 30 gauge needle, by securing an upwardly pointing needle within each tube 84 before the vacuum is drawn, or the like. Such a procedure relatively quickly produces a multi-well plate

with capillary holes without the need for employing an expensive injection mold. Further, since raw materials are cheaper, being only a sheet of plastic, the cost per plate is also reduced. Of course, the above-described method may be used with a standard commercial molding process, by including needles in the mold for a multiwell plate.

Holes may also be formed in custom-made or commercially-available multiwell plates, e.g., 96-well plates, (obtained from e.g., Polyfiltronics (Rockland, MA), Corning Costar (Oneonta, New York), Nalge Nunc International (Naperville, IL), and the like) by piercing the wells of such plates with a suitable needle. The needle is preferably fixed into a chuck such that only the tip (e.g., 0.5-5 mm) of the needle protrudes from the chuck. This facilitates the punching of similar or identical holes in a series of wells, by inserting the needle into a wall or bottom of a well until the chuck hits the wall or bottom of the well. The wells are preferably punched from the bottom of the plate, so that the dimensions of the holes at the inside of the wells can be better controlled. Further, punching from the bottom of the plates into the inside of the wells often results in small burrs surrounding the hole inside the well. Such burrs are advantageous because they help prevent spherical articles such as beads from clogging the capillary holes.

Exemplary non-circular holes may be formed using a needle (e.g., an ordinary sewing needle) that has been ground to have 3 or more facets along its shaft at its tip. Needles having a triangular cross-section are straight-forward to produce by grinding a round needle along 3 facets. Needles ground in this manner may be obtained, for example, from Step Tools Unlimited, Inc. (Santa Clara, CA). Non-circular holes may also be formed as slits. For example, an exemplary slit may be formed by piercing the bottom of a well with a razor blade, scalpel blade or other fine cutting edge.

Another method of forming non-circular capillary holes is by inducing cracks in the wells of the plate, in predetermined regions (e.g., in the bottom end), following the molding process. For example, the plates could be molded to have

bottoms tapering to a rounded apex, as shown in Figs. 8A and 8B, with the rounded apex being slightly thinner than the remainder of the plate. Upon being subject to a stress, e.g., rapid cooling, the rounded apex would crack, producing the requisite capillary holes.

The invention has now been described in detail. However, it will be appreciated that certain changes and modifications may be made. Therefore, the scope and content of this invention are not limited by the foregoing description. Rather, the scope and content are to be defined by the following claims.

Claims

1. A multiwell plate for handling articles suspended in a liquid, comprising:
a plurality of wells, with each well having a bottom end; and
a capillary hole in each of at least some wells of said plurality, the capillary hole being adapted to (i) retain articles in a well having said hole, and (ii) retain liquid in said well while said liquid is not subjected to extrinsic forces.

2. A plate as in claim 1, wherein the capillary hole is disposed in the bottom end of said well.

3. A plate as in claim 1, wherein the bottom end is tapered to an apex.

4. A plate as in claim 1, wherein the capillary hole has a non-circular profile.

5. A plate as in claim 4, wherein the capillary hole has a triangular profile.

6. A plate as in claim 1, wherein the capillary hole is disposed in a side of the well.

7. A plate as in claim 1, wherein said well includes only a single hole.

8. A plate as in claim 1, wherein the capillary hole has a limiting dimension that is between about 5μm and about 500 μm.

9. A plate as in claim 8, wherein the capillary hole has a limiting dimension that is between about 10μm and about 300 μm.

10. A plate as in claim 1, wherein liquid is retained in said well, in absence of extrinsic forces, by capillary forces.

11. A plate as in claim 1, wherein the hole is biased closed in absence of extrinsic forces.

12. A plate as in claim 1, wherein the plate contains 96 wells.

13. A plate as in claim 1, wherein the plate contains 864 wells.

14. A system for handling articles, the system comprising:
a multiwell plate of any of claims 1-13; and
a bottom plate having a plurality of holding vessels;
wherein the number of wells equals or exceeds the number of holding vessels such that when the multiwell plate is positioned above the bottom plate, each well is aligned with at least one holding vessel, wherein a fluid from wells having said capillary hole may be transferred into a corresponding holding vessel by application of an extrinsic force.

15. A system as in claim 14, wherein the extrinsic force is provided by centrifuging the plates.

16. A system as in claim 14, wherein the extrinsic force is provided by application of a vacuum under the multiwell plate.

17. A system as in claim 14, wherein the extrinsic force is provided by a piece of an absorbent material placed against the bottom ends of said wells.

18. A system as in claim 14, wherein each well is aligned with a separate holding vessel.

19. A system as in claim 14, wherein multiple wells are aligned with a single holding vessel.

20. A method for identifying compounds, the method comprising:
providing a multiwell plate of any of claims 1-13;
providing a bottom plate having a plurality of holding vessels;
introducing at least one article into at least some of the wells, with the article having a compound included thereon;
releasing the compound from each of the articles;
transferring at least a portion of the released compounds through the capillary holes and into at least one of the holding vessels of the bottom plate; and

performing assays on the compounds transferred from the wells to assess activity of the compounds.

21. A method as in claim 20, wherein the article is a solid support useful for performing solid-phase chemical or oligomer synthesis.

22. A method as in claim 20, wherein only a portion of the released compound is transferred into a holding vessel

23. A method as in claim 20, wherein the assays are performed in the holding vessels.

24. A method as in claim 20, wherein said transferring the released compounds through the capillary holes includes centrifuging the plates.

25. A fluid transfer system, comprising:

a donor member having a plurality of separate regions, with at least some of the regions containing at least one chemical composition, wherein the chemical composition at each region is distinct from any other chemical composition in the donor member;

an acceptor member having a plurality of defined locations which are each adapted to receive a liquid medium;

a transfer mechanism which directly and systematically transfers at least some of the chemical compositions from the donor member regions to at least some of the acceptor member locations such that the locale of each transferred chemical composition within the acceptor member is known; and

wherein the acceptor member locations each have a volume that is less than about 500 μl.

26. A system as in claim 25, wherein at least some of the regions contain at least one solid support having at least one of the chemical compositions thereon, and wherein the transfer mechanism transfers the chemical compositions from the donor member regions to the acceptor member locations after the release of the chemical compositions from the solid supports and while the solid supports remain within the donor member regions.

27. A system as in claim 26, wherein the chemical compositions are included within a liquid medium when transferred, and wherein the transfer mechanism comprises a valve that is disposed within each region.

28. A system as in claim 27, wherein:

said donor member is a multiwell plate;

said plurality of separate regions is a plurality of wells, with each well having a bottom end;

said transfer mechanism is a capillary hole in at least some of the wells, the capillary hole being adapted to (i) retain a solid support in a well having said hole, and (ii) retain liquid in said well by capillary forces while said liquid is not subjected to extrinsic forces; and

said acceptor member is a bottom plate having a plurality of holding vessels;

wherein the number of wells equals or exceeds the number of holding vessels such that when the multiwell plate is positioned above the bottom plate, each well is aligned with at least one holding vessel, wherein a fluid from wells having said capillary hole may be transferred into a corresponding holding vessel by application of an extrinsic force.

29. A system as in claim 25, wherein the donor member, the transfer mechanism and the acceptor member are isolated from the outside environment.

30. A system as in claim 25, wherein the acceptor member includes at least four locations per square centimeter.

31. A system as in claim 25, wherein the donor member regions each have a volume that is less than about 500 μl.

32. A method for combining distinct chemical compositions with reagents, the method comprising:

providing a plurality of solid supports having the chemical compositions thereon;

organizing the solid supports having the chemical compositions thereon into separate regions of a donor member so that each region includes a distinct chemical composition;

releasing at least some of the chemical compositions from their solid supports while within the donor member regions;

systematically transferring at least some of the released chemical compositions to individual locations within an acceptor member such that the locale of each transferred chemical composition within the acceptor member is known, and wherein the individual locations define a volume that is less than about 500 μl; and

introducing a reagent to each location having one of the chemical compositions.

33. A method as in claim 32, further comprising maintaining the solid supports within the donor member regions while transferring the released chemical compositions to the acceptor member locations.

34. A method as in claim 32, wherein the chemical compositions are released into a liquid medium prior to transferring the chemical compositions to the acceptor member locations.

35. A method as in claim 32, wherein the donor member regions and the acceptor member regions are organized into two dimensions arrays.

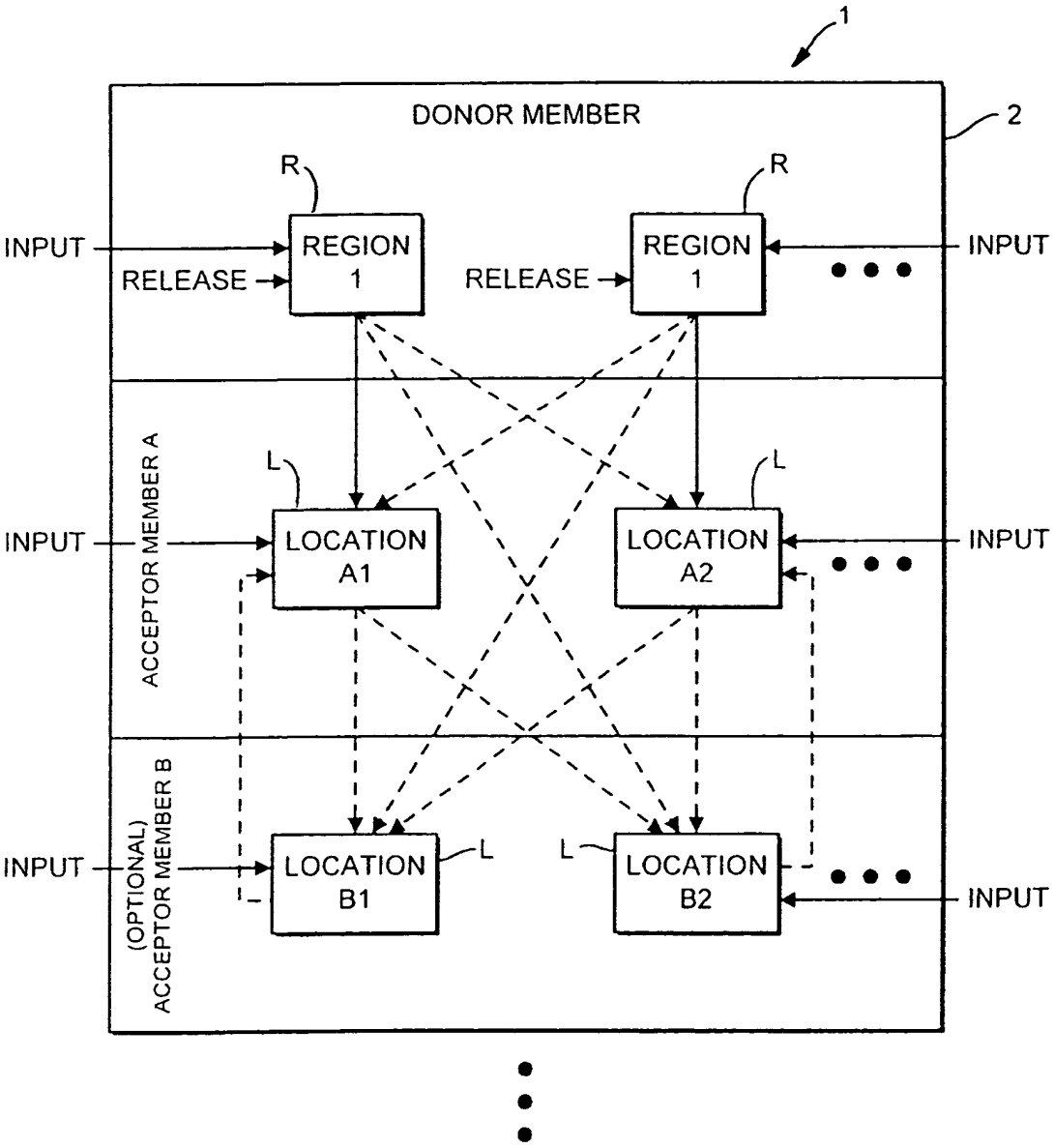

1
DONOR MEMBER
2
R
R
INPUT
RELEASE
REGION 1
RELEASE
REGION 1
INPUT
L
L
INPUT
LOCATION A1
LOCATION A2
INPUT
ACCEPTOR MEMBER A
(OPTIONAL) ACCEPTOR MEMBER B
INPUT
LOCATION B1
L
L
LOCATION B2
INPUT

FIG. 1

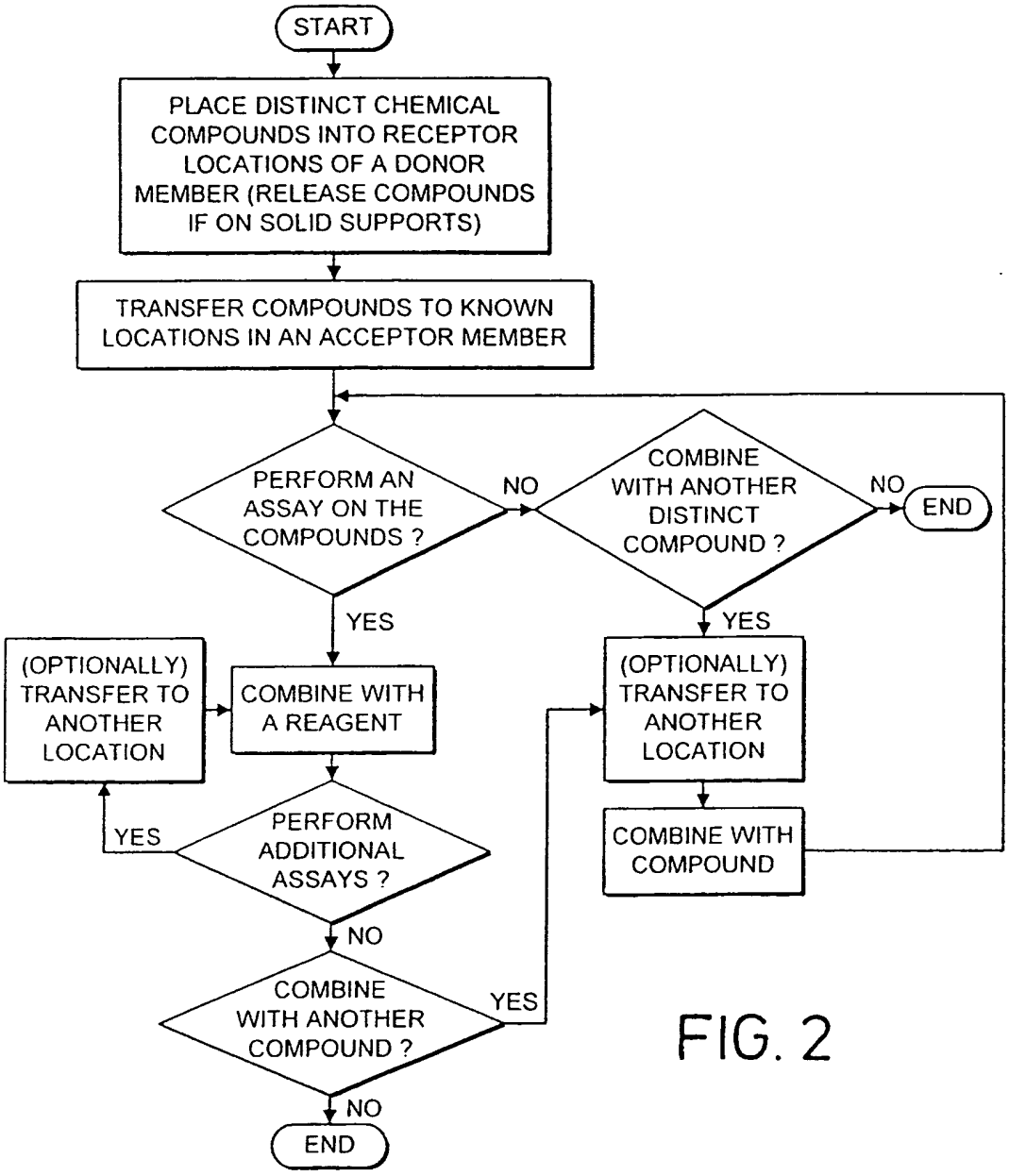

START
PLACE DISTINCT CHEMICAL COMPOUNDS INTO RECEPTOR LOCATIONS OF A DONOR MEMBER (RELEASE COMPOUNDS IF ON SOLID SUPPORTS)
TRANSFER COMPOUNDS TO KNOWN LOCATIONS IN AN ACCEPTOR MEMBER
PERFORM AN ASSAY ON THE COMPOUNDS ?
NO
COMBINE WITH ANOTHER DISTINCT COMPOUND ?
NO
END
YES
YES
(OPTIONALLY) TRANSFER TO ANOTHER LOCATION
COMBINE WITH A REAGENT
(OPTIONALLY) TRANSFER TO ANOTHER LOCATION
YES
PERFORM ADDITIONAL ASSAYS ?
COMBINE WITH COMPOUND
NO
COMBINE WITH ANOTHER COMPOUND ?
YES
NO
END

FIG. 2

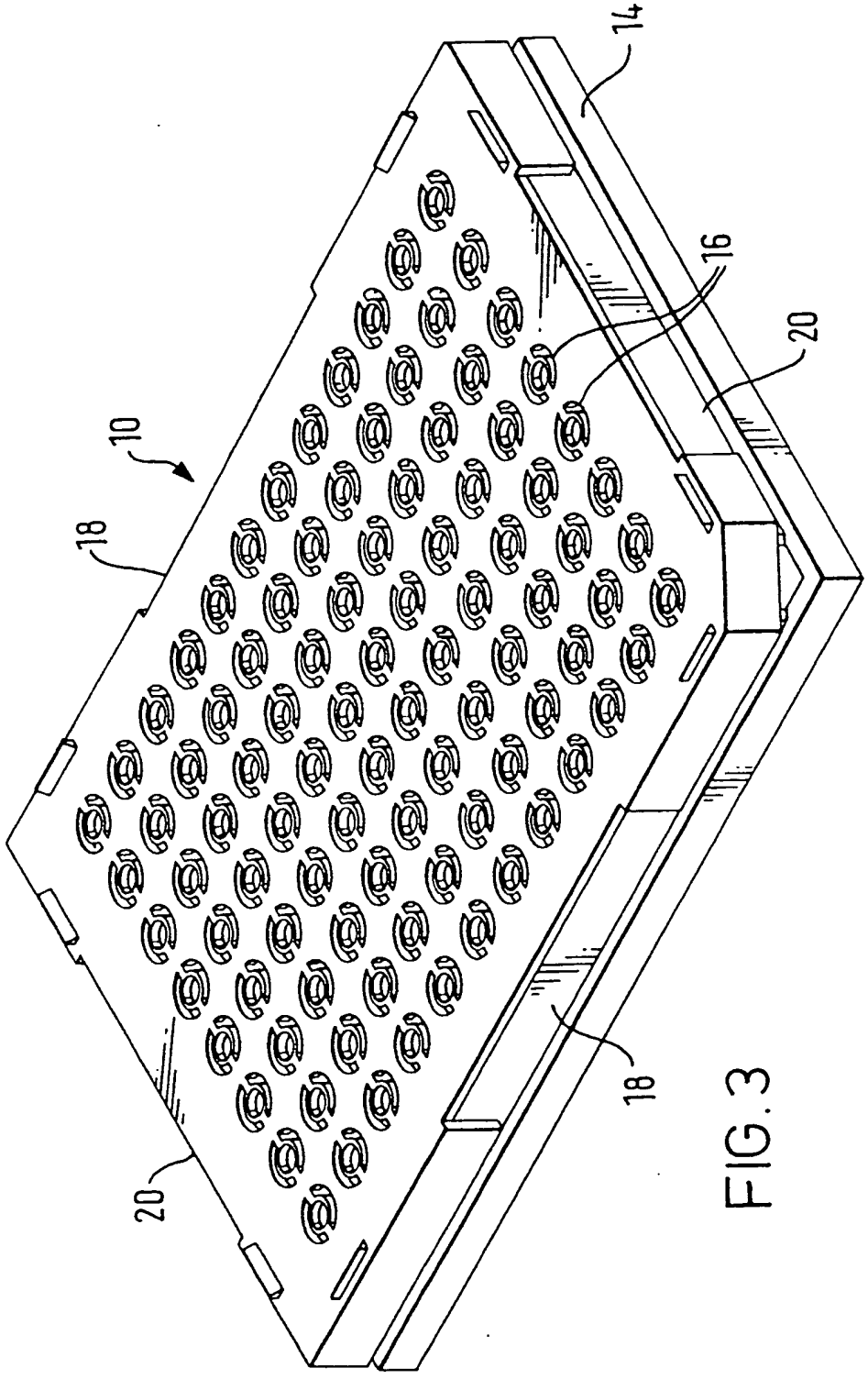


FIG. 3

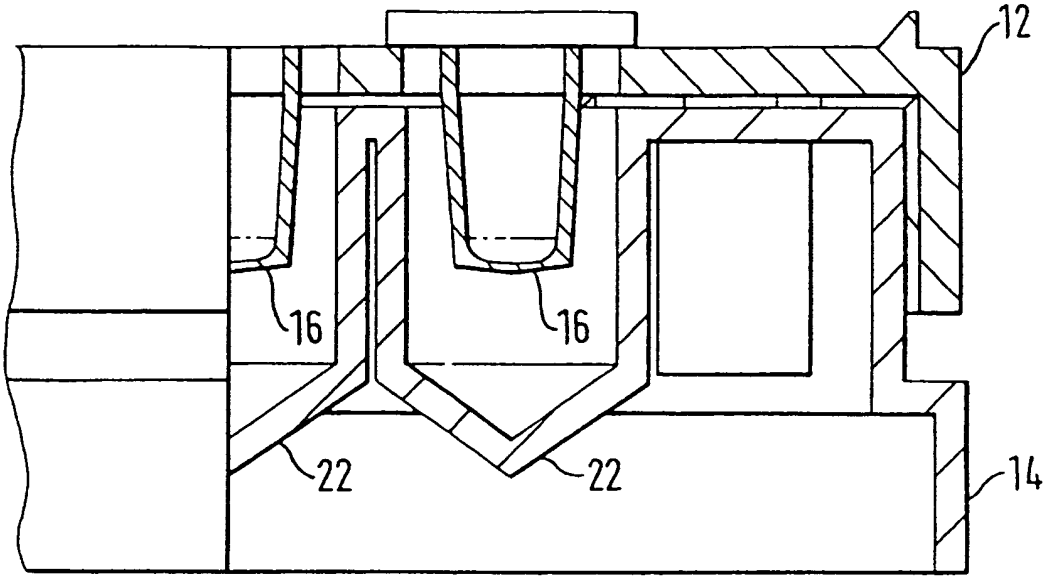


FIG. 4

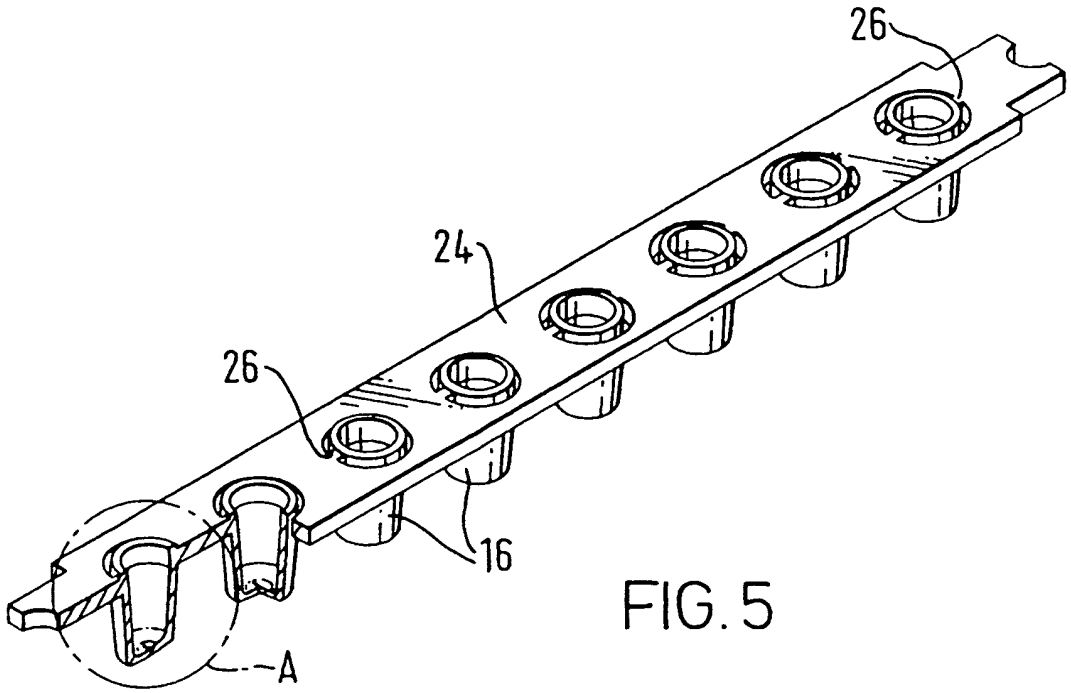


FIG. 5

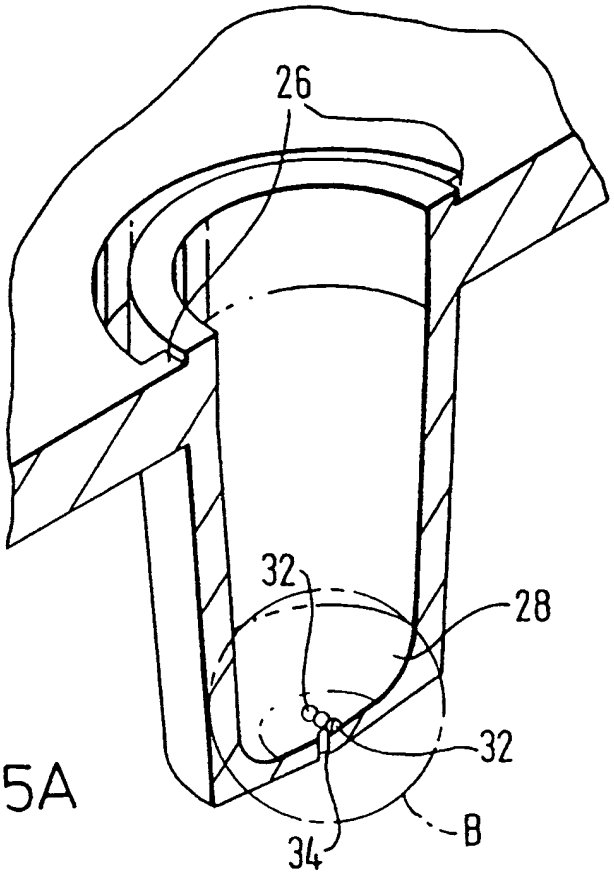


FIG. 5A

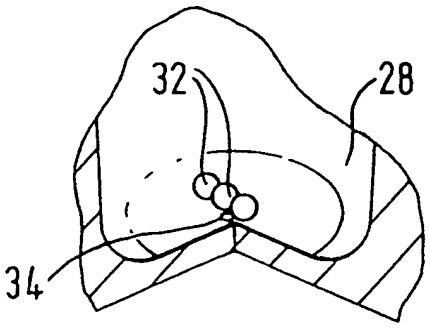
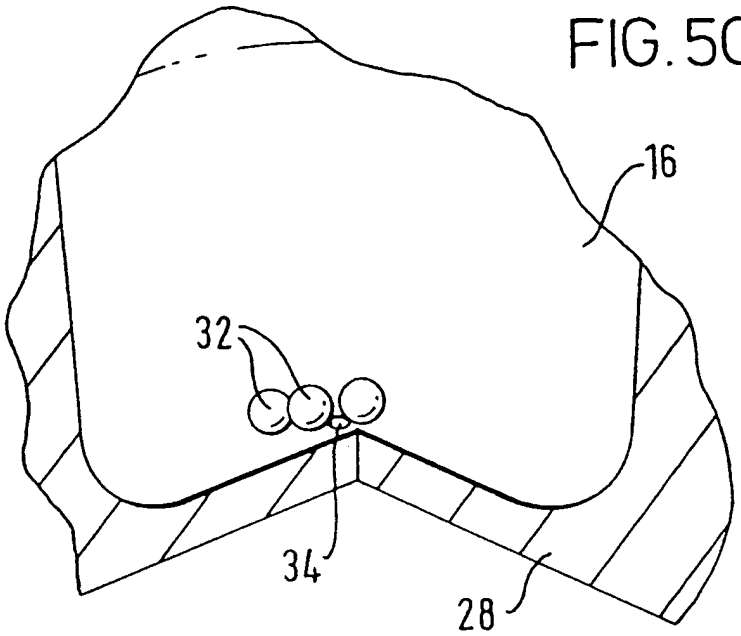


FIG. 5B

FIG.5C



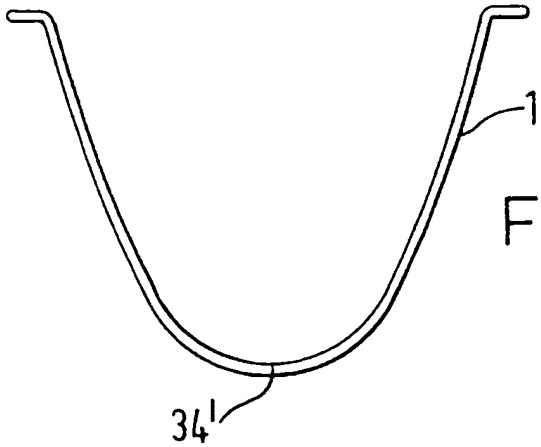


FIG.5D

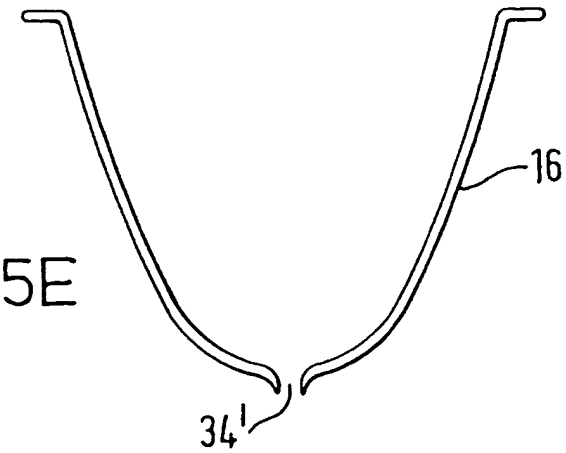


FIG.5E

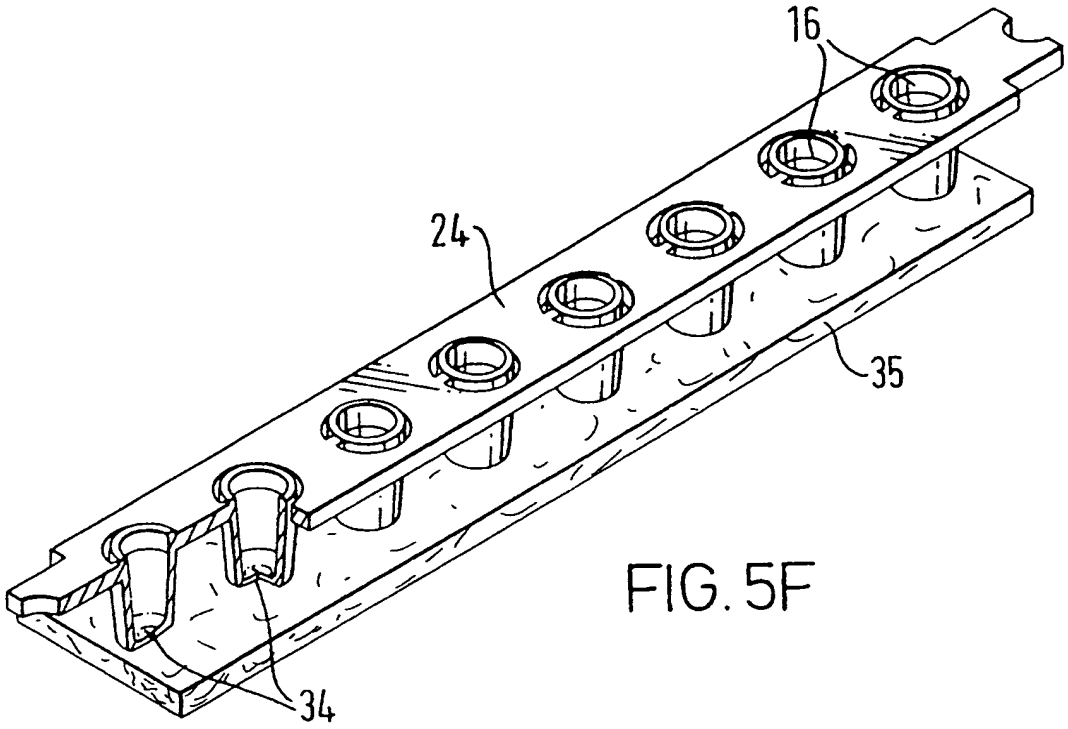


FIG. 5F

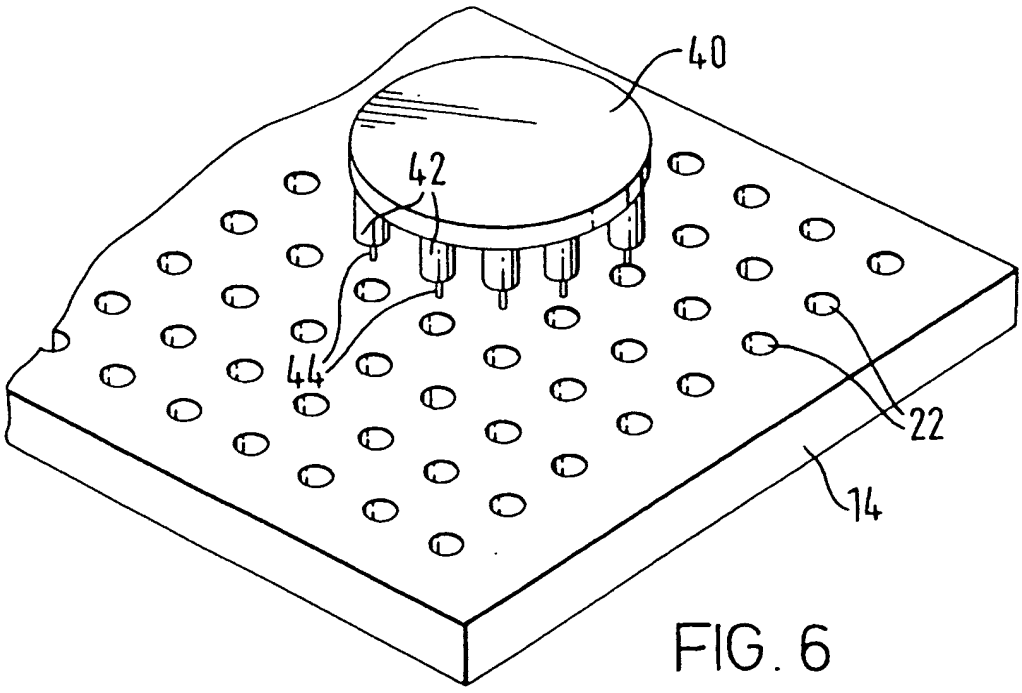


FIG. 6

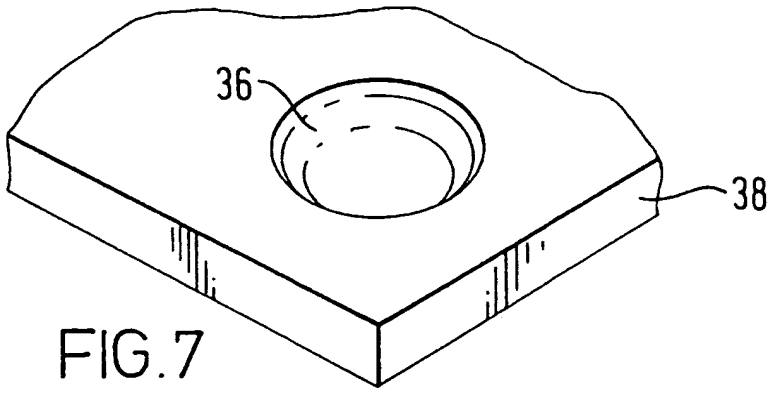


FIG.7

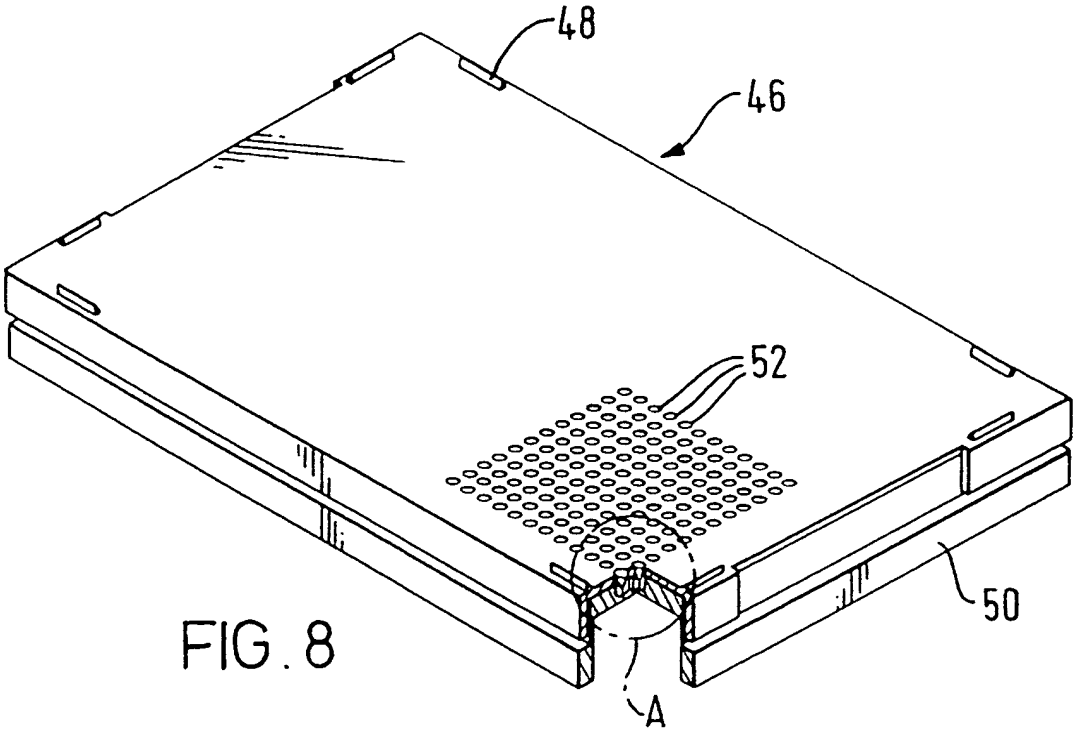


FIG.8

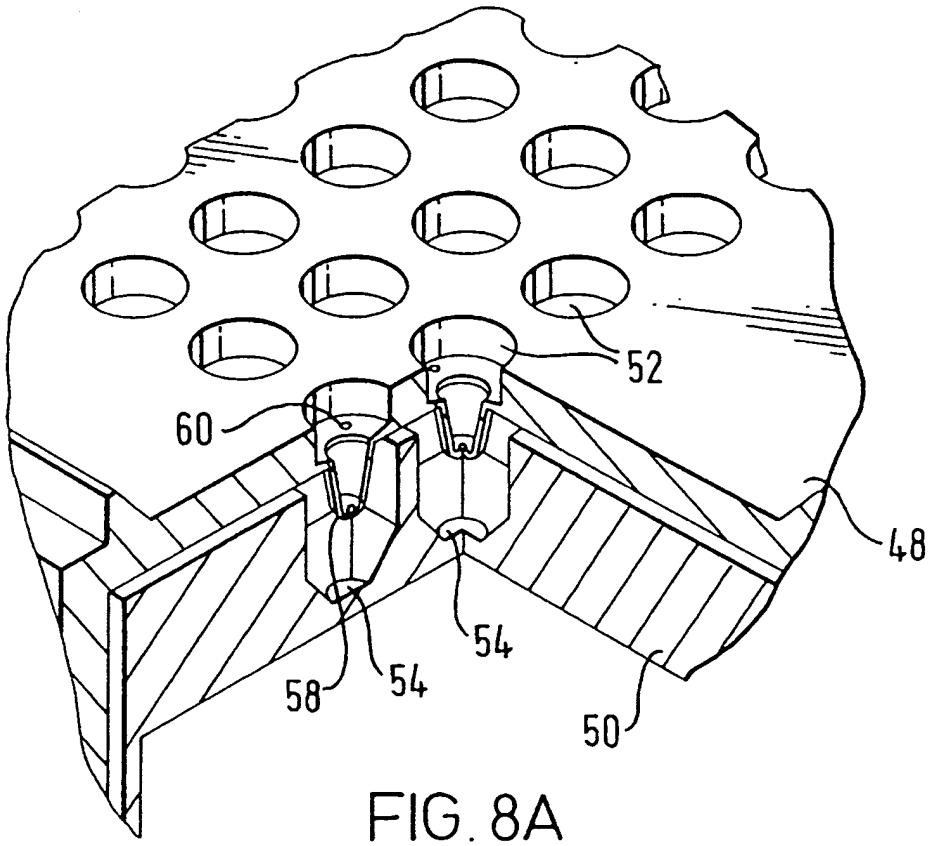


FIG. 8A

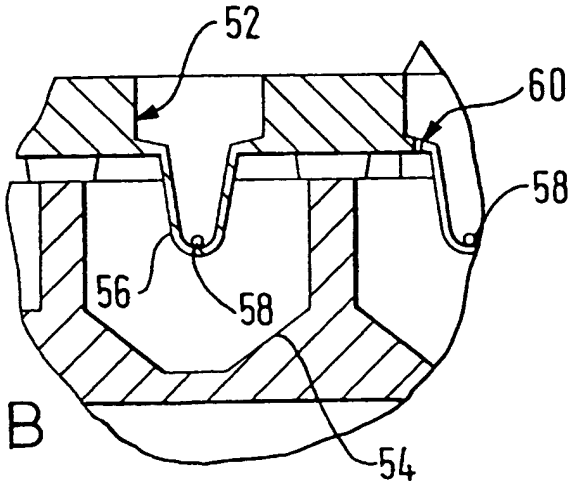


FIG. 8B

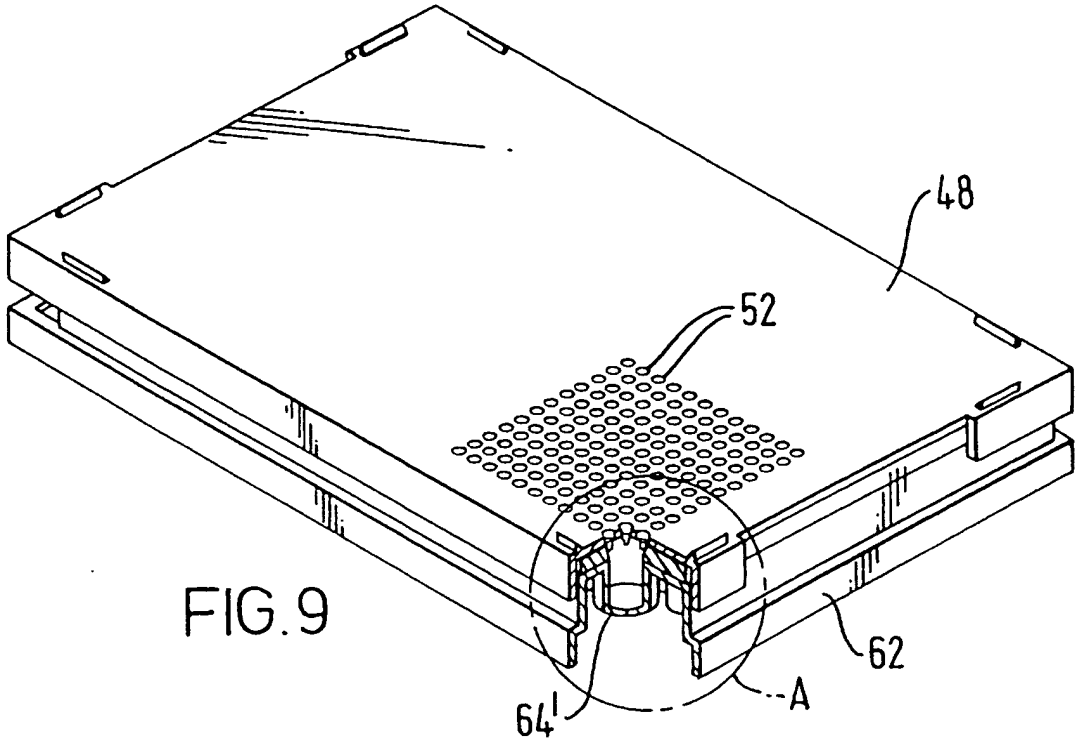


FIG.9

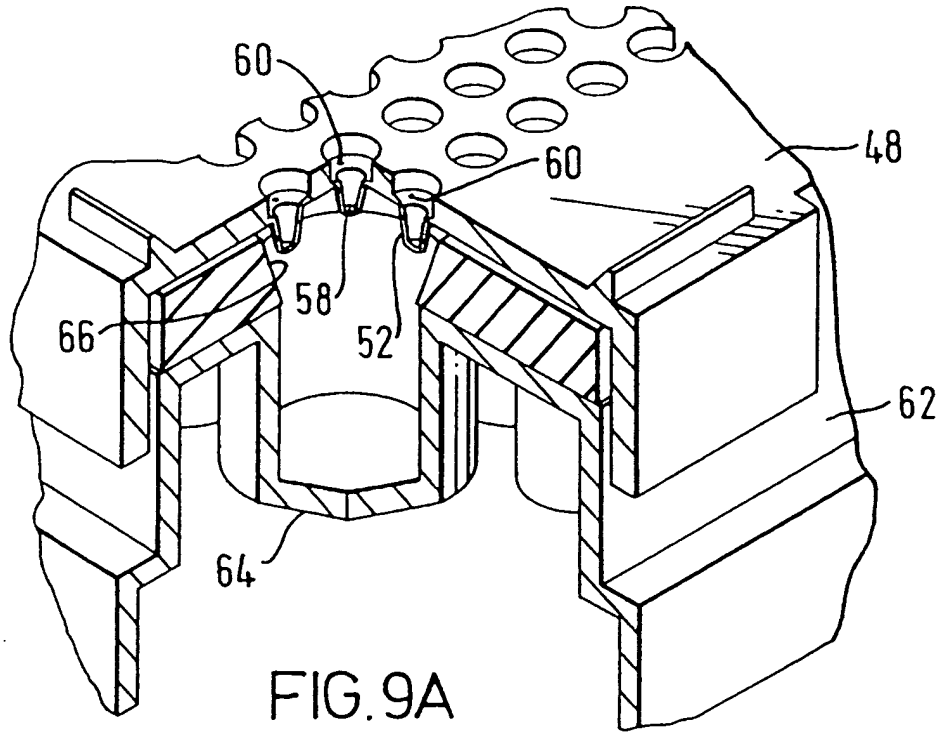


FIG.9A

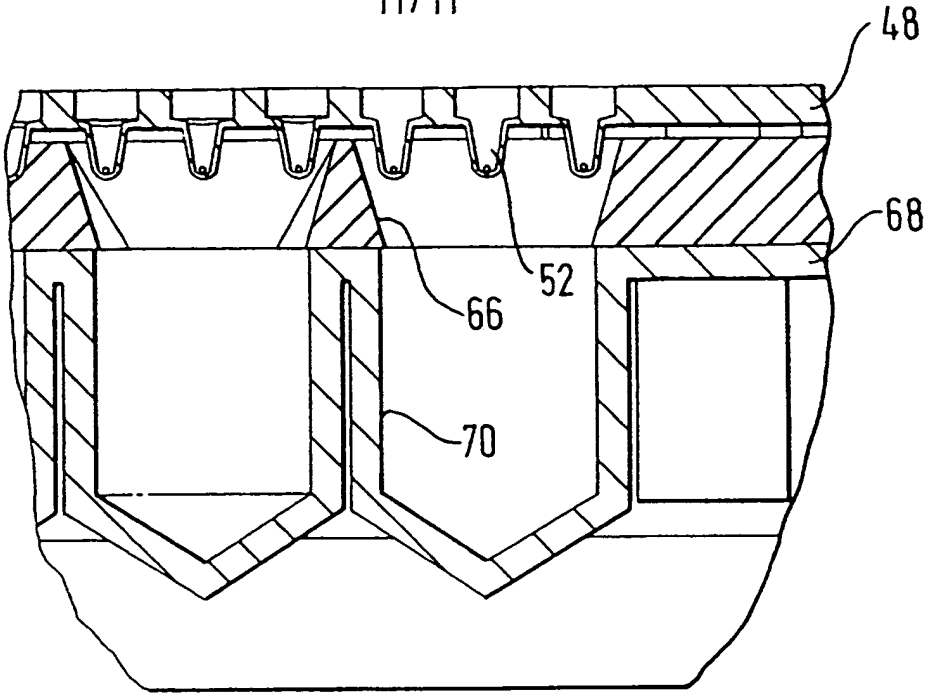


FIG.10

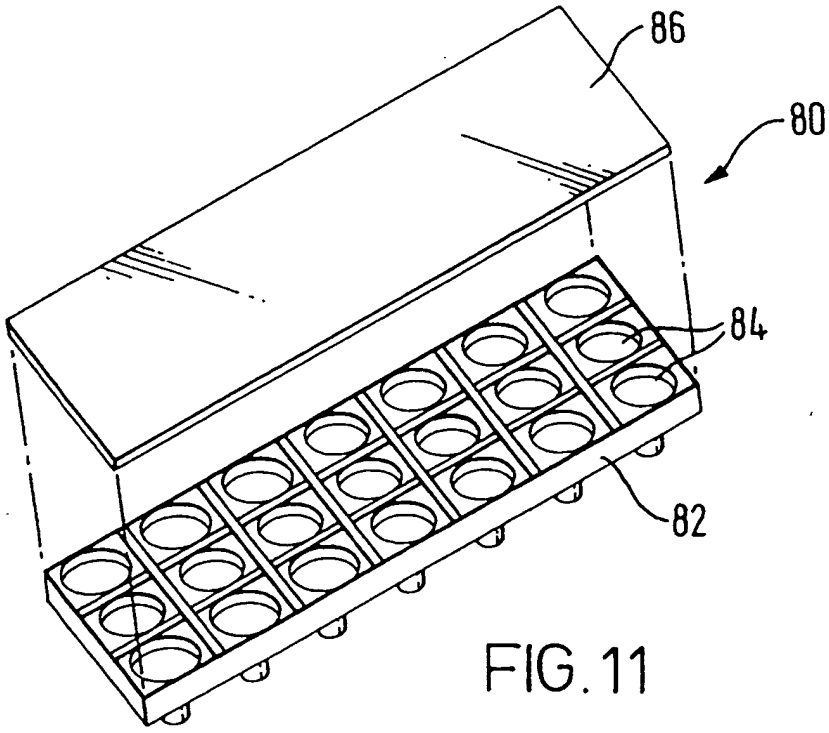


FIG.11

INTERNATIONAL SEARCH REPORT

Intc onal Application No
PCT/GB 97/03298

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 B01J19/00 B01L3/00

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 B01J B01L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 11262 A (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY) 27 April 1995 see abstract see page 6, line 22 - page 9, line 7 see page 11, line 25 - page 12, line 4 see page 20, line 3 - page 24, line 4 see page 25, line 9 - line 24 see page 29, line 24 - line 36 see page 31, line 12 - line 24 see figures 5-7	1,2,7,8, 10-12, 14,16, 18, 20-23, 25-29, 31-35
A	--- -/--	9,13

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

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1

Date of the actual completion of the international search	Date of mailing of the international search report
2 March 1998	11/03/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stevnsborg, N

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INTERNATIONAL SEARCH REPORT

Inte ɔnal Application No
PCT/GB 97/03298

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category ³	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 90 02605 A (M.MELDAL ET AL.) 22 March 1990 see abstract see page 6, line 24 - page 7, line 24 see page 12, line 30 - page 13, line 15 see page 14, line 3 - line 14 see claims; figure 3	1,2,7, 10-12
A	---	
X	US 5 273 718 A (SVEN-ERIK SKÖLD & KENT ANDERSSON) 28 December 1993 see the whole document	1,2,7, 10,11, 14,18, 20,21,23
A	---	
A	US 4 111 754 A (HYDOW PARK) 5 September 1978 see the whole document	1-35

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INTERNATIONAL SEARCH REPORT

..nformation on patent family members

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